UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,682	01/06/2006	Mark T. Gladwin	4239-67618-05	3411

36218 7590 01/06/2009

KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
01/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,682	GLADWIN ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *16-19,24-28 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,20-23,29-32,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-40 are pending. Claims 16-19 and 24-28 have been withdrawn as being directed to non-elected subject matter. Claims 29-40 are new. Of the new claims, claims 33-38 are withdrawn from consideration because they are dependent upon withdrawn claims. Therefore, claims 1-15, 20-23, 29-32, 39 and 40 are under examination. Applicant has amended the claims and submitted a new IDS which resulted in a new ground of rejection. Accordingly, this Action is FINAL.

Withdrawn rejections:

Applicant's amendments and arguments filed 10/20/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Henderson et al. (Abstract; Lancet 1972, 300(7788), pp 1162-1163) is withdrawn because the subject is not known to have a medical condition associated with the cardiovascular system. Gale (US 4,849,226) is withdrawn because Gale discloses topical/transdermal administration and not the instantly claimed routes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15, 20-23, 29-32, 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. Claim 1 recites: “a medical condition associated with the cardiovascular system”. The word “association” renders the claim indefinite because iIt is unclear what the nature of the association might be. It could be directly associated with the cardiovascular system such as pertaining to the blood vessels or heart or it could be indirectly associated with the cardiovascular system such as a vascularized tumor or malaria. Thus the nature of the medical condition becomes a guessing game. Therefore, the Examiner comes to the conclusion that the metes and bounds of the claim are blurry and because of that the claims are indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-4, 9, 11, 12, 20, 29-32 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Zapol (WO 94/00180).

Zapol discloses use of NO or a source thereof for the purpose of manufacturing a medicament for use in therapy to decrease or prevent contraction of a smooth muscle in a hollow organ, such as an eye, of an animal, such as man, by introducing an effective amount of NO (claims 1 and 5). The Examiner is interpreting the use to mean a method of treating. When one looks to the specification to find a definition of “a source thereof” one finds on page 16, line 33, inorganic nitrite, NO2-. It inherently has a

pharmaceutically acceptable counter cation. The nitrite is not acidified. When one looks to find out how the NO is introduced to the eye to treat vasoconstriction of the eye (which is associated with the cardiovascular system) one finds on page 19, line 8-14 that it can be directly injected into the fluid of the eye which reads on intraocular injection. Therefore, the Examiner reasonable concludes that all the limitations of instant claims 1, 9, 11 and 12 are disclosed by the reference. Vasoconstriction reads on a condition associated with decreased blood flow and anticipates instant claim 20. Since the compound is the same as instantly claimed it inherently reacts with hemoglobin to release NO and anticipates instant claim 2. Note that claim 1 is drawn to an effective amount of non-acidified nitrite. Since the same effective amount of nitrite is used it inherently induces production in the subject of no more than about 25% methemoglobin and anticipates instant claim 3. Since the same effective amount of nitrite is used it inherently induces production in the subject of no more than about 3% methemoglobin and anticipates instant claim 4. The same reasoning is applied to the limitations of instant claims 29-32. Please note that the U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics. When as here, the prior art appears to contain the exact same effective amount of ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 20-23, 29-32, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Abstract: J. Cereb. Blood Flow Metab. 1994, 14(2), 217-26) in view of Modin et al. (Acta Physiol Scand 2001, 171, 9-16 and,with respect to claims 13-15, Nachtsheim (West J Med. 1998, 169(2), 112-113).

Applicant claims a method for treating a subject having a medical condition associated with the cardiovascular system inducing vasodilation and/or increasing blood flow in a subject, comprising administering to the subject an effective amount of a non-acidified pharmaceutically-acceptable salt of nitrite for a sufficient period of time to induce vasodilation and/or increase blood flow in the subject thereby treating the subject, wherein the administration is by a route selected from the group consisting of

intravenous injection, intramuscular injection, oral, buccal, rectal, ex vivo, intraocular, intraperitoneal, intravenous, intraarterial, subcutaneous, inhalation, intramuscular, and into a cardiopulmonary bypass circuit.

Determination of the scope and content of the prior art

(MPEP 2141.01)

In the Abstract, Zhang et al. teach the use of **nitric oxide donors** to increase blood flow and reduce brain damage in focal **ischemia** (title). Zhang et al. teach the nitric oxide donors sodium nitroprusside (3 mg/kg/h) and 3-morpholino-sydnonimine (1.5-6 mg/kd/h) administered into the carotid artery (intraarterial) of rats for 60 min. Zhang et al. teach and suggest that nitric oxide donors may represent a new therapeutic strategy for the management of acute stroke.

Modin et al. teach that nitric oxide is derived from nitrite (title). Modin et al. teach that the relaxatory effect of nitrite was increased at pH 6.6 over neutral pH (Abstract). Thus Modin et al. teach that **non-acidified nitrite** also has relaxatory effects similar to "acidified" nitrite (see figures 1, 2, figure 5 and respective discussion in the text). Modin et al. administered various amounts of **sodium nitrite** but noted a threshold response of 10 microM and near relaxation to basal tone at 1000 microM for the non-acidified sodium nitrite (page 11, Results). Modin et al. teach adding additional agents (ascorbic acid) to enhance the effect of the sodium nitrite (Abstract) Modin et al. conclude that inorganic nitrite evokes vasodilation most likely through nitric oxide release and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during **ischemia**/hypoxia (page 15, last paragraph).

Nachtsheim teaches that **sildenafil** is a known promoter of vasodilation that can enhance sexual experience (see whole article). Nachtsheim teaches that sildenafil works in conjunction with nitric oxide to enhance the vasodilatory effect. Nitric oxide signals cGMP production which then causes smooth muscle relaxation. Sildenafil blocks the enzyme responsible for degradation of cGMP thus leading to higher sustained levels of cGMP and relaxation of the smooth muscle (Page 112).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Zhang et a. is that Zhang et al. do not expressly teach non-acidified sodium nitrite in the amount of 0.6 to 240 microM. These deficiency in Zhang et al. is cured by the teachings of Modin et al.

2. The difference between the instant application and Zhang et a. is that Zhang et al. do not expressly teach addition of sildenafil in the method. These deficiency in Nachtsheim.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use non-acidified sodium nitrite within the range instantly claimed, as suggested by Modin et al., in the method of Zhang et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because : 1) Zhang et al. suggest using other nitric oxide donors; and 2) Modin et al. suggest how much sodium nitrite, a known nitric oxide donor, would be beneficial for use in tissues during ischemia. Modin et al. teach carotid injection over 60 minutes of the sodium nitrite and other forms of administration such as parental, oral, bucal, rectal, ex vivo, or intraocular, peritoneal, intravenous, intraarterial, subcutaneous, inhaled, intramuscular or cardiopulmonary bypass circuit modes of adminstation are not only obvious to one of ordinary skill in the art of medicine but also merely result in the same thing; increasing the blood plasma levels of sodium nitrite, in the absence of evidence to the contrary. It is the Examiner's position that rats render obvious other mammals such as humans to one of ordinary skill in the art of medicine.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use sildenafil, as suggested by Nachtsheim, in the method of Zhang et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is established that sildenafil enhances the action of nitric oxide thus presenting an improved treatment protocol for the patient with the added benefit of potential enhanced sexual activity for the patient.

Summary: The ***concept*** of treating cerebral ischemia with nitric oxide donors to induce vasodilation and/or increase blood flow is established in the art. Non-acidified sodium nitrite is known to be a nitric oxide donor in the art. Applicant has merely followed the suggestions of Zhang et al. and Modin et al. to use sodium nitrite in the

treatment of cerebral ischemia. The predictable expected result is induced vasodilation and increased blood flow in the subject.

From recent case law: "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." (KSR INTERNATIONAL CO. v. TELEFLEX INC. ET AL. 550 U. S. ____ (2007) page 24).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant asserts that "nitric oxide donors" and sodium nitrite are not equivalent substitutes for each other and then compares the empirical formulas for sodium nitrite, SNP and SIN. Of course the empirical formulas are different because these are different

chemical entities. The common thread that binds them together is that they are all nitric oxide progenitors albeit by different mechanisms.

Applicant asserts that there is no such evidence on record that that inorganic nitrite salt is an equivalent substitute for SNP or SIN. Respectfully, the Examiner cannot agree. These materials are known sources of NO. As explained above, Modin et al. conclude that inorganic nitrite evokes vasodilation most likely through nitric oxide release. Thus the cited art recognizes inorganic nitrite as a source of NO.

Applicant asserts that the reference of Lauer et al. teaches away from sodium nitrite did have a vasodilatory effect in vivo and that others in the art were skeptical of Applicants data. If the Examiner were to agree with this line of reasoning then an enablement rejection would be forthcoming. Since Lauer et al. teach the same concentrations as instantly claimed then how can Lauer et al. state that nitrite lacks intrinsic vasodilatory action and yet Applicant claims vasodilitory action? The skepticism appears to be over native concentration of nitrite but Applicant is claiming up to 240 micormolar which is orders of magnitude above maximal eNOS production (see remarks, page 15 of 18).

It appears to the Examiner that experimental protocol is critical to the observations made in the art. Given the differences between the studies it is extremely difficult if not impossible to provide a proper comparison. This is especially true given the preponderance of literature related to nitric oxide as evidenced by the massive IDS's filed by Applicant. Having weighed the evidence at hand, it is the Examiner's position that the data of Modin showing a vasodilating effect of non-acidified nitrite at pH 7.45 provides concrete data that sodium nitrite is a progenitor of NO at that pH no matter where that pH might be located. Given that blood pH is about 7.35 to 7.45 then one would has a reasonable expectation that sodium nitrite acts as a vasodilator through the action NO at that pH as well. The Examiner cannot control the influence of other factors in the experiments. The fact is that nitrite at pH 7.45, which is the same pH as blood, acts as an NO donor.

Respectfully, Applicant's arguments are not persuasive and the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-13, 20-23, 39 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, and 9-15 of copending Application No. 10/563,683. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the instant invention embraces or is embraced by the subject matter of the copending application. One of ordinary skill in the art would recognize the methods in the copending application of treating brain ischemia-–reperfusion (medical conditions associated with the cardiovascular system) by decreasing blood pressure and or increasing vasodilation with a non-acidified sodium nitrite to a subject. The same concentrations of sodium nitrite (0.6 to 240 micromolar) are claimed as well as the subjects and routes of administration (intravenous and inhalation).

The copending application does not expressly teach treating a subject having a medical condition associated with the cardiovascular system.

However, one of ordinary skill in the art would have recognized cardiac ischemia reperfusion and cerebral artery vasospasm as medical conditions associated with the cardiovascular system.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to arguments:

Applicant requests that the rejection be held in abeyance until allowance. Until that time, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 10/20/08 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 6:15-3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Examiner, Art Unit 1616